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10/537,971	06/09/2005	Yoshihiro Ohmiya	SAEG189.001 APC	8735

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EXAMINER	
NOAKES, SUZANNE MARIE	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
09/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/537,971	OHMIYA ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *09 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/12/05, 6/16/06 & 8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 16 and 17, drawn to a method of measuring the processing ability *of a protein* (of claims 1-12), in the reply filed on 15 June 2007 is acknowledged. Claims 1-5 and 18-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

The restriction requirement is deemed proper and therefor is made Final.

Status of the Application

2. Claims 1-21 are pending in the instant application, as noted above, claims 1-15 and 18-21 are withdrawn from further consideration. Claims 16 and 17 are subject to examination on the merits.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 28 August 2006, 16 June 2006 and 12 September 2005 has been considered by the examiner. See initialed and signed PTO-1449's.

It is noted that two documents cited on the IDS from 28 August 2006 have not been considered as they have not been filed with the Office: EP 1 265 990 and EP 1 088 233. Rather, two other WO documents have been filed but are not listed on the IDS: WO 01/68824 and WO 99/66324.

Specification and/or Drawings

4. The disclosure and/or drawings are objected to because of the following informalities regarding compliance with the sequence rules.

Compliance with Sequence Rules

5. The sequence listing, filed in computer readable form (CRF) and paper copy on June 9, 2005, has been received and entered. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

I. The following Figures contain sequences that contain four or more consecutive amino acids or ten or more nucleic acids without any corresponding SEQ ID NO: and/or no reference to any SEQ ID NO: in the Brief Description of the Drawings.

a) In Figure 1, contains multiple amino acid sequences that are four or more amino acids in length without any corresponding sequence identifier.

b) In Figure 2, shows multiple amino acid and nucleic acid sequences without any corresponding sequence identifier.

II. The specification contains sequences that are not sequence compliant:

a) Page 4, line 28, contains a peptide sequence without a corresponding sequence identifier.

b) It is unclear if EYFP, listed o p. 7, line 6, is meant to represent the amino acids Glu-Tyr-Phe-Pro. If so, a corresponding sequence identifier is missing. Applicants are asked to clarify this.
c) Page 8, line 12, contains a peptide sequence without a corresponding sequence identifier.

* If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Appropriate correction is required.

Claim Objections

6. Claims 16 and 17 are objected to because of the following informalities: The claims are dependent upon non-elected and withdrawn claims. In addition, the lciams contain non-elected subject matter which has been withdrawn from consideration (e.g. measuring the processing ability of DNA according to claims 13-15). Applicants must rewrite said claims in independent form so as to include all of the limitations of the non-elected claims and to omit the non-elected subject matter contained therein.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description:

8. Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for measuring the processing ability of a certain cell characterized by introducing a monitor protein (from claims 1-12) into the cell and measuring the change in energy transfer of the protein. The protein(s) used in the method, which is introduced into various cells to determine if said cells are capable of processing the 'monitor protein' or not, encompass are large and variable genus of proteins. The scope of the genus encompassed within the claims range from any monitor protein having a protein cleave sequence (which can be anything) and a "property variable region" which exhibits a change in luminescence and fluorescence upon processing (see claim 1) or that of the more limited SEQ ID No: 2. However, it is noted that SEQ ID No: 2 itself encompasses its own variable and diverse genus having multiple and separate species having one or more amino acid substitutions, deletions, insertions etc. (see claim 11). However, the only specific species encompassed within

the scope of the claims and which is in the specification which is exemplary of the entire broad and variable genus is SEQ ID No: 2 itself. The specification makes clear that even for those encompassed within SEQ ID No: 2, there is considerable variation (see specification, p. 6, lines 7-29 which states:

> The present specification further discloses the following invention.
>
> I. Proteins showing in the following (1) to (4):
>
> (1) a monitor protein represented by an amino acid sequence in SEQ ID NO:2;
>
> (2) a monitor protein wherein a sequence or a position in a region cleaved by processing and a property variable region (a luminescent protein and a fluorescent protein) is changed in the amino acid sequence in SEQ ID NO:2;
>
> (3) a monitor protein wherein a processing cleavage region figured by an underline in the amino acid sequence in SEQ ID NO:2 (amino acid sequence of 18 amino acid residues including a cleavage point of prepronocistatin protein) is substituted with 10 to 100 amino acid residues, preferably 20 to 40 amino acid residues in the vicinity of a processing cleavage site; and
>
> (4) a monitor protein wherein a property is variable in a property variable region due to a change of a three dimensional structure in the vicinity of the processing cleavage region. The monitor protein wherein a luminescent protein and a fluorescent protein are arranged with sandwiching the processing region, the energy transfer from the luminescent protein to the fluorescent protein is not effected before and after the processing, and thus a luminescent color is changed is suitable.

Other multiple embodiments are encompassed on pages 3-4, points 1-12 (see also claims 1-12). Thus, there are numerous species having significant diversity in structure and function of the proteins sequences. However, in many embodiments, the claims require no structure function relationship whatsoever, just a function requirement. In those embodiments which envision SEQ ID No: 2 with multiple additions, deletions and mutations/substitutions, (which is should be noted, that the limitation "represented by

SEQ ID No: 2" also encompasses mutations, deletions and substitutions because "represented" by is not limiting. "Represented by" is interpreted merely as being a symbolic representation of many other species.), the single disclosed species of SEQ ID No: 2 is not sufficiently representative of the many different species encompassed by any or all the broad genus' to which the claims are drawn.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. Finally, it is noted that the courts have also established that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

Thus, the description of single species encompassed with the broad genus of monitor protein molecules described above, which also have no structure-function correlation, is not deemed representative of the broad genus of molecules to provide evidence of possession for the entire scope of the genus or proteins being claimed.

Enablement:

9. Claims 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for measuring a processing ability of a certain cell by introducing monitor proteins into a cell and evaluating the change in energy. However, there is no description whatsoever in the specification of how one skilled in the art would "introduce" said protein back into a cell. Because the claims are drawn solely to the use of the protein and not the DNA, presumably, the only way in which one skilled in the art could "introduce any of the monitor proteins according to claims 1 to into the cell" would be to add a protein transduction domain (such as HIV-1 Tat, polylysine, Antp22, protein transduction domain sequences) which allows said protein to translocate various cellular membranes and enter into a cell. However, there is nothing described in the specification regarding this aspect of the invention or how introducing said protein is to take place and there is nothing in the prior art to teach or suggest to one skilled in the art of how one is introduce a protein into a cell other than by using the DNA and not the protein. All of the examples in the specification are drawn to using the DNA to introduce said protein into a cell, and all of the relevant references listed on the IDS citing numerous prior art (see for example Houle et al. or Waud et al.) also use the DNA in order to practice the claimed methods, and not solely the protein as has been

elected by Applicants. Furthermore, there is no clear or reasonable expectation that even if one skilled in the art did make a monitor protein with a protein transduction domain attached to traverse the cellular membrane and enter said cell, where that protein would actually end up. If it ends up in an undesirable place, said protein usually unfolds (e.g. if it ends up in the cytosol and does not prefer a reducing environment) or becomes degraded. Thus, in order for one skilled in the art to practice this invention, considerable undue experimentation would be required and even then there is an uncertainty regarding the expectation of success.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As noted, the claims are drawn to introducing the protein, not the DNA into a cell or a cell derived from a human. However, introducing proteins into any cells, whether human, CHO,.*E. coli*, etc., requires either using the DNA to transform said cells which then over express the given protein (however, as noted, this is then drawn to using the DNA and not the protein) or alternatively, using a leader sequence attached to the monitor protein in order for said protein to gain entry into said cell. However, the amount of direction and guidance in the specification is unclear regarding this information. For instance, p. 12 (last line) to p. 13 state that a monitor protein of the present invention can be obtained by incorporating a gene of the present invention into a vector and expressing it in a host cell, for example *E. coli* BL21 cells. Alternatively, one can express the proteins for instance in COS7 mammalian cells (see p. 14). Thus, for instance with the limitations of claim 17, how would one get the protein from *E. coli* into a derived human cell without isolating said protein and adding a protein transduction domain? The state of the prior art seems to rely upon using the DNA to transform cells that express the protein, however, the claims are drawn to introducing "a monitor protein of any or claims 1-12", many of which have no known corresponding DNA sequences described anywhere. Furthermore, the prior art is of no assistance as is also is directed to specifically using DNA and not the protein and the working examples suffer from the same deficiency. As noted, the predictability of introducing the monitor proteins encompassed with the claims into any cells and subsequently being

able to evaluate said cells ability to process said foreign protein in dubious at best considering the limitations in translocating said membranes and the proteins not being degraded by the cells machinery.

All of these factors leave the conclusion that there would be considerable undue experimentation for a skilled artisan to practice the claimed invention and furthermore the predictability of success would likely be limited.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suzanne M. Noakes

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Art Unit 1656